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(Towards education)

July 23, 2015-.

TOWARDS EDUCATION IN THE HISTORY OF NEUROPSYCHOPHARMACOLOGY

Part 4

The Sharon Unit in Massachusetts, USA

Discoveries in neuropsychopharmcology that have not been followed up and experiments that could not be replicated

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There was an exponential growth in neuropychopharmacology research during the last four decades of the 20th century with many promising findings which were not followed up and experiments which could not be replicated.

An example of a *discovery that has not been followed up* is Frank Fish's. In the early 1960s, Fish, in a study that included 474 patients with schizophrenia, found significant differences in responsiveness to neuroleptics in the different forms and sub-forms of schizophrenia using Karl Leonhard's "classification of endogenous psychoses" (Fish 1964; Leonhard 1957). The differences were so great, that in one group, affect-laden paraphrenia, one of the three forms of unsystematic schizophrenia in Leonhard's classification, more than 4 in 5 patients responded markedly or moderately to treatment, whereas in another group, systematic hebephrenia, one of the three categories of systematic schizophrenia, less than 1 in 4 patient responded. Fish published his results, in 1964s, in Encephale, but his findings have not been followed up to-date.

The differences in responsiveness to neuroleptic in the different forms of schizophrenia in were not restricted to therapeutic effects but were present also in susceptibility to adverse effects (Ban 1990). Findings of an international survey carried out by Ban, Guy and Wilson, in the 1980s showed that the prevalence of tardive dyskinesia was over 20% in the treatment refractory subpopulation of patients with "systematic schizophrenia" in Leonhard's classification, and below 5% in the treatment responsive subpopulation of patients with

"unsystematic schizophrenia" (Ban,. Guy, Ban and Wilson published their results in 1985 and 1986 but in spite of important clinical implications no attention was paid to their report.

Another *finding with important clinical implications that has not been followed up* is David Janowsky's. In the early 1970s, Janowsky, El-Yousef, Davis and Sekerke were administering physostigmine, a cholinesterase inhibitor which causes acetylcholine to increase, to see whether it could turn off antidepressant-induced confusional states, thinking that these states were induced by the anticholinergic effect of antidepressant drugs. Janowsky also had the idea that physostigmine might also turn off mania. The concept was, as he reminisced 20 years later in an interview with Leo Hollister, "that like the heart, there could be a balance between adrenergic and cholnergic factors in mania and depression with mania being too little acetylcholne and too much norepinephrine or other monoamines and depression being converse. Indeed, we found that mania in several patients was turned off rapidly and dramatically by physostigmine. Over a period of minutes depression was induced. From that I proposed the adrenergic-cholinergic hypothesis of mania and depression, published first (in 1972) as a letter in Lancet" (Janowsky 2011; Janowsky, El-Yousef, Davis, Sekerke 1972).

Experiments which could not be replicated far outnumber findings which have not been followed up in neuropsyochopharmacological research, and some of the stories about such experiments , as for example the story of Robert Haim Belmaker, adopted here from Belmaker's interview by Joseph Calabrese, is quite educational (Belmaker 2011). The story begins with Belmaker's acceptance in NIMH's clinical associate program and joining Dick Wyatt, who just took over Bill Polin's laboratory that was focused on genetic research including twin studies. Wyatt already had his "finding" of low platelet monoamine oxidase (MAO) in schizophrenia at the time Belmaker arrived and to find out whether low platelet MAO is a genetic marker, he asked Belmaker to get hold of Pollin's twin register and take blood samples from all the twins for platelet MAO. The idea was that if in both twins MAO activity was low it was a genetic marker but if only in the ill twin was low, then it was a marker for schizophrenia. The collection of blood samples was completed in six months and yielded a paper in Science the same year (1973) suggesting that low platelet MAO is a marker for schizophrenia (Belmaker et al 1974; Murphy, Belmaker and Wyett et al 1974; Wyett et al1973). After leaving NIMH and setting up his laboratory in Israel, the first thing Belmaker did was to develop an assay for MAO activity in

platelets. To make a long story short, he could not replicate the original finding that monoamine oxidase activity is low in the platelets of schizophrenic patients (Belmaker et al 1976; Murphy et al 1977). Yet, through the nineteen seventies and eighties there were about fifty papers on MAO in platelets of schizophrenics. Most people didn't find low MAO activity in schizophrenic patients, but a few did. For Belmaker the finding of low MAO in platelet of patients with schizophrenia was an "accident".

The primary objective of the Sharon Unit is to contribute to the foundation of INHN's educational program in the history of the field by identifying "discoveries" in neuropsychopharmacology research that were not followed up, and experiments that could not be replicated. In order to achieve its objective, the Unit, directed by George Gardos, is expected to generate, in collaboration with network members, two chronological lists: one for discoveries which have not been followed up, and another for experiments which could not be replicated. Another responsibility of the Unit is the facilitation of interaction about entries on both lists.

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July 23, 2015